Attorney Docket No. 80451

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of: Maurice Petitou, et al.

Patent No.: 4,818,816

Granted: April 4, 1989

Serial No. 115,593

Filing Date: October 26, 1987

For: PROCESS FOR THE ORGANIC SYNTHESIS OF OLIGOSACCHARIDES AND DERIVATIVES THEREOF

CERTIFICATE UNDER 37 C.F.R. 1.10(b)

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Date of Deposit: 1-29-02

I hereby certify that this paper is being deposited with the United Stated Postal Service "Express Mail Post Office to Addressee" Service on the indicated above and is addressed to: Commissioner for Patents, Box Patent Extension, Washington, DC 20231

Geraldine D Shi

Name

January 29, 2002

Date

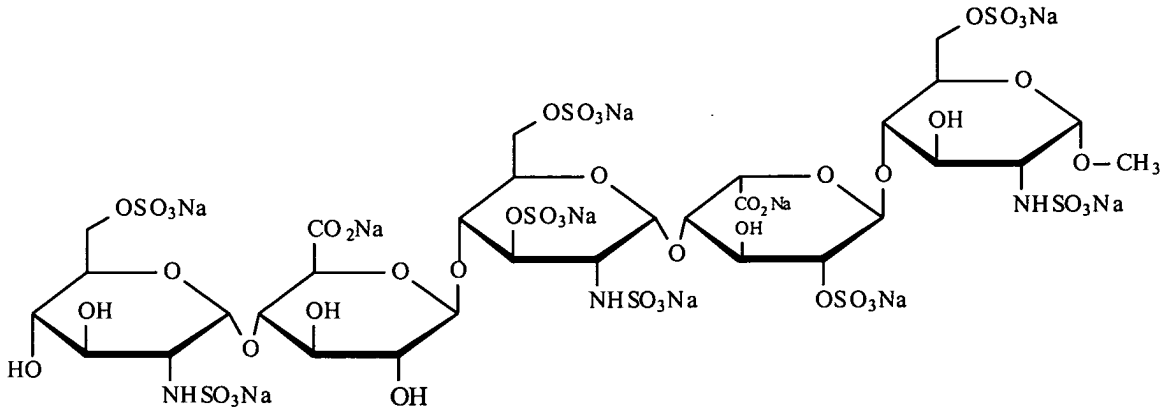
Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 AND 37 C.F.R. §1.740

Dear Sir:

Under the provisions of 35 U.S.C. §156 and in accordance with 37 C.F.R. §1.740, Sanofi-Synthelabo, the owner of the entire right, title, and interest in United States Patent 4,818,816 which claims fondaparinux sodium, hereby requests that the term of said patent, originally expiring on August 19, 2003 pursuant to a terminal disclaimer, be extended 1,116 days to expire on September 8, 2006. The chain of title of United States Patent 4,818,816 from the inventors to Sanofi-Synthelabo is attached hereto as Exhibit 1.

(1) Fondaparinux sodium is the generic name of the compound having the chemical name methyl *O*-2-deoxy-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-D-glucopyranuronosyl-(1→4)-*O*-2-deoxy-3,6,-di-*O*-sulfo-2-(sulfoamino)-α- D-glucopyranosyl-(1→4)-*O*-2-*O*-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranoside, decasodium salt, and having the structural formula:



(2) Fondaparinux sodium was subject to regulatory review by the Food and Drug Administration (FDA) under Sections 505(i) and 505(b) of the Federal Food, Drug and Cosmetic Act.

(3) Fondaparinux sodium, having the tradename ARIXTRA®, was approved for commercial marketing or use by the Food and Drug Administration under Section 505(b) of the Federal Food, Drug and Cosmetic Act on December 7, 2001.

(4) The active ingredient in the approved product is fondaparinux sodium. Fondaparinux sodium has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

(5) This application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application can be submitted is February 5, 2002.

(6) The patent for which an extension is being sought is United States Patent 4,818,816, issued April 4, 1989, in the name of Maurice Petitou, Jean-Claude Jacquinet, Pierre Sinay, Jean Choay, Jean-Claude Lormeau, and Mahmoud Nassr, and having an expiration date of August 19, 2003 pursuant to the terminal disclaimer filed October 23, 1988.

(7) A complete copy of United States Patent 4,818,816, including the entire specification, claims, and drawings, is attached hereto as Exhibit 2.

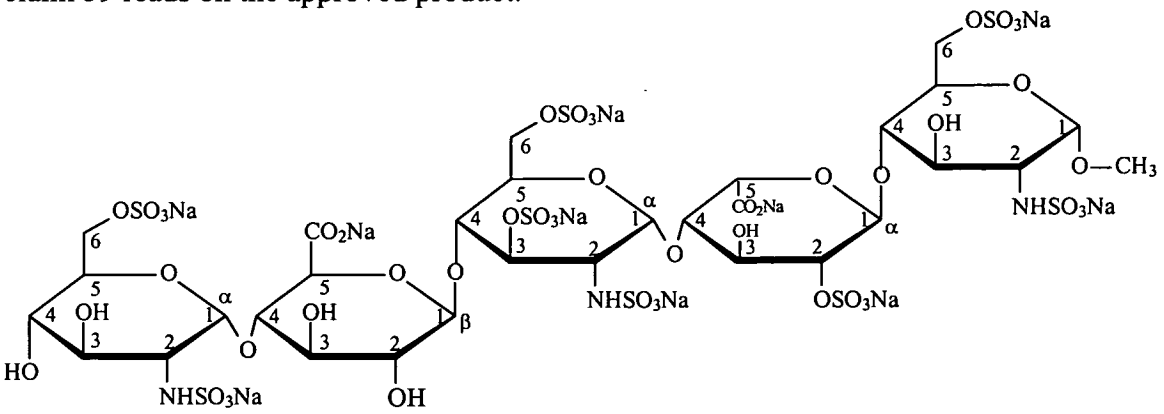
(8) Copies of the following documents in United States Patent 4,818,816 are attached hereto as Exhibits 3, 4, and 5:

(a) the Terminal Disclaimer filed October 23, 1988 (Exhibit 3);
(b) the Certificate of Correction issued December 17, 1991 (Exhibit 4); and
(c) the Maintenance Fee Record and the Maintenance Fee Statements showing payment of the 4th, 8th, and 12th year maintenance fees (Exhibit 5).

No Reexamination Certificate has been issued for this patent.

(9) United States Patent 4,818,816 claims the product fondaparinux sodium and a process for the manufacture thereof. Claims 56, 58, and 59 read on fondaparinux sodium, and claims 36-39 read on a method for the manufacture thereof. Certain process steps in the manufacture of fondaparinux sodium are also read on by claims 1, 2, 11-14, 19, 22, 23, 25-27, 29-35, 40, and 43.

The structural formula of fondaparinux sodium and the table hereinbelow demonstrate how claim 59 reads on the approved product.

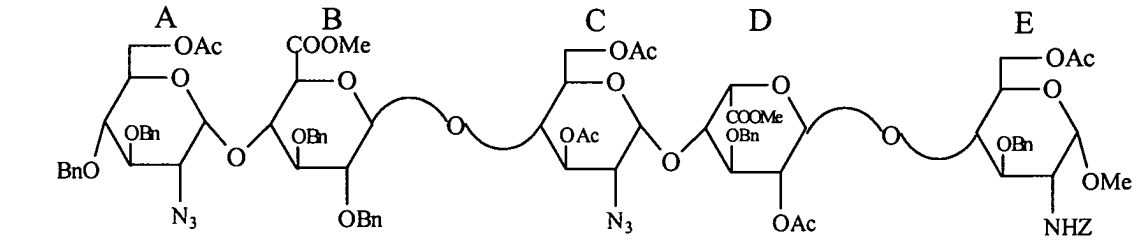


A, C, E = D-glucosamine; B = D-glucuronic acid; D = L-iduronic acid

Elements of Claim 59	Structural elements of fondaparinux sodium
oligosaccharide of a single structure comprised of 2-12 alternating D-glucosamine and uronic acid units	pentasaccharide of the above structure comprised of alternating D-glucosamine units A, C, and E and uronic acid units B and D
uronic acid units are selected from D-glucuronic acid and L-iduronic acid	B is a D-glucuronic acid D is an L-iduronic acid
OSO_3 groups are positioned at any but not all of carbons 3 and 6 of the D-glucosamine units and carbons 2 and 3 of the uronic acid units	OSO_3 groups at carbon 3 of D-glucosamine unit C and carbon 6 of D-glucosamine units A, C, and E, and at carbon 2 of uronic acid unit D
linkages between D-glucosamine and uronic acid are of the 1-4 alpha type	linkages between D-glucosamine A and uronic acid B and between D-glucosamine C and uronic acid D are 1-4 alpha
linkages between L-iduronic acid and D-glucosamine are of the 1-4 alpha type	linkage between L-iduronic acid D and D-glucosamine E is 1-4 alpha
linkages between D-glucuronic and D-glucosamine are of the 1-4 beta type	linkage between D-glucuronic acid B and D-glucosamine C are 1-4 beta

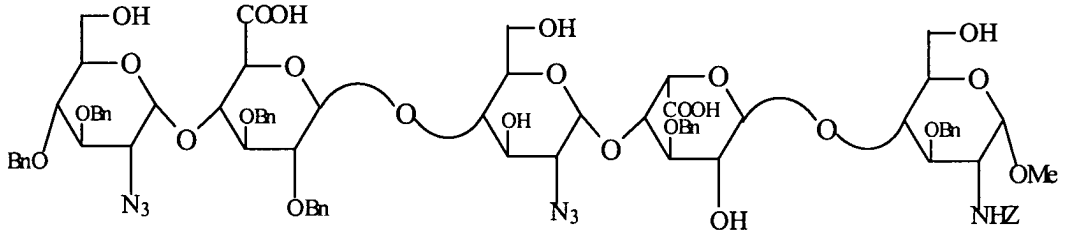
The reaction scheme, which shows the method of manufacturing fondaparinux sodium, and the table hereinbelow demonstrate how claim 37, which ultimately depends from claim 31 through intermediate dependent claim 36, reads on the method for manufacturing the approved product.

Manufacture of Fondaparinux Sodium

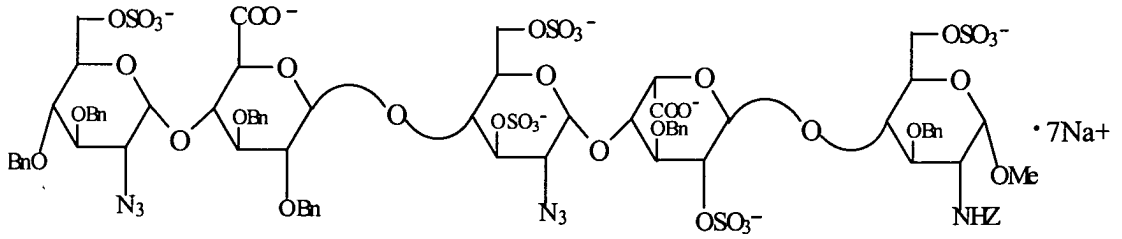


Ac = acetyl, Bn = benzyl, Me = methyl, Z = benzyloxycarbonyl

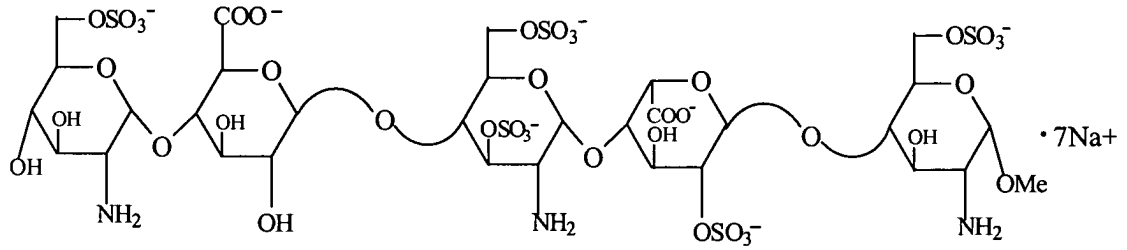
↓ [1]



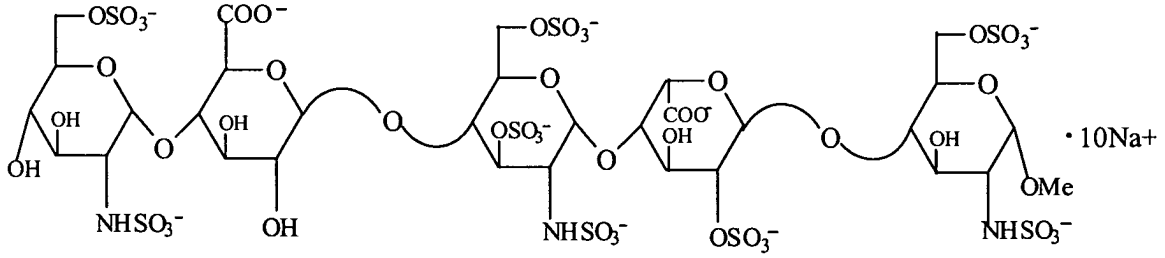
↓ [2]



↓ [3]



↓ [4]



fondaparinux sodium

Elements of Claim 37	Manufacture of Fondaparinux Sodium
protected polysaccharide of 2-12 alternating D-glucosamine and uronic acid units having semi-permanent protecting groups, permanent protecting groups, other protecting groups which form an ester at the uronic acid carboxyl groups, and nitrogen containing groups at carbon 2 of the D-glucosamine units	protected polysaccharide of 5 alternating D-glucosamine (A, C, E) and uronic acid (B, D) units having semi-permanent protecting groups (Ac), permanent protecting groups (Bn), protecting groups which form an ester at the uronic acid carboxyl groups (Me), and nitrogen containing groups at carbon 2 of the D-glucosamine units (N_3 and NHZ)
subjected to a process comprising the steps of	subjected to the process comprising steps [1]-[4] of the above reaction scheme
removing the semi-permanent protecting groups	step [1]
introducing functional groups selected from OSO_3 groups and OPO_3 groups in place of the semi-permanent protecting groups	step [2]
removing the permanent protecting groups and converting the nitrogen containing groups to amine groups	step [3]
substituting the amine groups with a group selected from SO_3 and acetyl	step [4]

10.) Fondaparinux sodium was subject to a regulatory review period consisting of (a) the period beginning on August 18, 1996, the effective date of Investigational New Drug (IND) Application No. 51,126 submitted July 19, 1996 (cross-referenced in IND No. 51,196 submitted July 31, 1996) under Section 505(i) of the Federal Food, Drug and Cosmetic Act and ending on February 15, 2001, the initial submission date of New Drug Application (NDA) No. 21-345 under Section 505(b) of the Federal Food, Drug and Cosmetic Act and (b) the period beginning on February 15, 2001, the initial submission date of NDA No. 21-345 and ending on December 7, 2001, the date the NDA was approved.

(11) The significant activities undertaken by or on behalf of Applicant and responses by the FDA during the applicable review period with respect to the approved product are as follows:

SUMMARY OF ARIXTRA® (FONDAPARINUX SODIUM)
IND AND NDA ACTIVITIES

IND 51,126 ACTIVITIES

Date	Activity
19 July 1996	Submitted original IND application (IND 51,126) (SN000)
24 July 1996	Organon authorized Sanofi to refer to IND 51,126 in IND 51,196 (SN001)
01 August 1996	Sponsors' minutes of 12 June 1996 FDA pre-IND meeting (SN002)
09 August 1996	Organon response to FDA's 16 July 1996 pre-IND meeting minutes letter (SN003)
13 August 1996	Telephone contact: Meeting minutes, submission of 09 August 1996
15 August 1996	Telephone contact: Additional discussion of meeting sponsor meeting minutes submitted 09 August 1996
18 August 1996	IND effective date
19 August 1996	FDA request for information
21 August 1996	Organon reply to differences between 12 June 1996 meeting and 15 August 1996 teleconference (SN004)
28 August 1996	FDA response to 21 August 1996 letter
29 August 1996	Telephone contact: Follow up to meeting minute discrepancies
09 October 1996	Information Amendment: 1 Pharm/Tox report (SN007)
10 December 1996	Information Amendment: 1 Pharm/Tox report (SN010)
28 January 1997	FDA request for information
14 March 1997	Response to FDA information request dated 28 January 1997 (SN013)
09 April 1997	Response to 28 January 1997 information request
23 April 1997	Information Amendment: 2 Pharm/Tox reports (SN017)
19 May 1997	Information Amendment: 3 Pharm/Tox reports (SN018)
05 June 1997	General Correspondence: clinical report (SN019)
18 June 1997	Organon Request for FDA input
25 June 1997	Organon request for FDA input
27 June 1997	Telephone contact: FDA information request
09 July 1997	Response to 27 June 1997 information request (SN023)
24 July 1997	Organon & FDA Teleconference to resolve 25 & 27 June 1997 request for FDA input
29 July 1997	Information Amendment: 1 Pharm/Tox report (SN025)
07 August 1997	FDA minutes of 24 July 1997 teleconference
06 November 1997	Information Amendment: 8 Pharm/Tox reports (SN034)
18 November 1997	Response to FDA's input from 24 July 1997 teleconference (SN036)
05 December 1997	Information Amendment: 2 Pharm/Tox reports (SN037)
08 January 1998	Information Amendment: 1 Pharm/Tox report (SN040)
21 January 1998	FDA Information Request

Date	Activity
13 February 1998	Information Amendment: 2 Pharm/Tox reports and 1 Clinical report (SN042)
26 February 1998	Organon response to FDA 21 January 1998 information request (SN043)
06 March 1998	Information Amendment: 2 Pharm/Tox reports and 4 Clinical reports (SN044)
27 March 1998	End of Phase II Meeting
13 April 1998	Organon minutes of 27 March 1998 End-of-Phase II meeting (SN047)
23 April 1998	FDA minutes of 27 March 1998 End-of-Phase II meeting . FDA information request.
08 May 1998	Information Amendment: 2 Clinical reports (SN049)
09 June 1998	General Correspondence: Sponsors' response to differences in the meeting minutes of the 27 March 1998 End-of-Phase II meeting (SN051)
26 June 1998	FDA Letter clarification to minutes of 27 March 1998 End of Phase II meeting
30 June 1998	Information Amendment: 1 Pharm/Tox report (SN054)
01 July 1998	FDA request for information
09 July 1998	FDA request for information
21 July 1998	Information Amendment: 5 Pharm/Tox summary reports (SN056)
24 July 1998	FDA recommendations and information requests
28 July 1998	Response to 09 July 1998 FDA information request (SN057)
28 July 1998	Information Amendment: CMC (SN058)
10 August 1998	Partial response to 24 July 1998 information request (SN059)
18 August 1998	FDA recommendations/requests
19 August 1998	Response to 01 July 1998 FDA information request (SN060)
19 August 1998	FDA request for information
20 August 1998	Telephone contact: Clarification FDA 19 August 1998 request for information
28 August 1998	Telephone contact: Additional discussion of FDA 19 August 1998 request for information
01 September 1998	Completed response to 24 July 1998 FDA recommendations and requests (SN061)
02 September 1998	Information Amendment: 1 Pharm/Tox report (SN062) Partial response to 19 August 1998 FDA request for information.
01 October 1998	Information Amendment: 2 Pharm/Tox reports (SN064) Partial response to 19 August 1998 FDA request for information.
06 October 1998	Information Amendment: 1 Pharm/Tox report (SN065) Partial response to 19 August 1998 FDA request for information.
16 October 1998	Information Amendment: Tabular report, statistical overview and data listings for Pharm/Tox report (SN066) Completes response to 19 August 1998 FDA request for information.
06 November 1998	Information Amendment: 1 Pharm/Tox report and 2 Clinical reports (SN068)

Date	Activity
10 November 1998	Information Amendment: 1 Pharm/Tox report (SN069)
02 December 1998	FDA recommendations and requests
10 December 1998	Information Amendment: 1 Pharm/Tox report (SN071)
04 January 1999	Information Amendment: CMC (SN074)
20 January 1999	Response to 23 April 1998 request for information (SN076)
25 January 1999	Information Amendment: 2 Pharm/Tox reports (SN077)
09 February 1999	End-of-Phase II Meeting. FDA Information request.
12 February 1999	Sponsors' minutes of 09 February 1999 End-of-Phase II Meeting (SN079)
26 February 1999	Information Amendment: 1 Pharm/Tox report (SN080)
03 March 1999	FDA Minutes of 09 February 1999 End of Phase II meeting.
04 March 1999	Response to 18 August 1998 recommendations/requests (SN081)
22 March 1999	Response to 09 February 1999 information request. (SN083)
30 April 1999	Information Amendment: 1 Pharm/Tox report (SN087)
08 September 1999	Information Amendment: 2 Pharm/Tox reports and 1 Clinical report (SN091)
21 January 2000	Information Amendment: CMC (manufacturing information) (SN098)
03 March 2000	Information Amendment: 1 Pharm/Tox report (SN103)
30 March 2000	FDA request for information
11 April 2000	Information Amendment: 1 Pharm/Tox report; (SN106)
27 April 2000	Information Amendment: 2 Pharm/Tox reports (SN107)
16 May 2000	Information Amendment: 2 Pharm,/Tox reports; (SN108)
15 June 2000	Response to 30 March 2000 FDA request for information (SN110)
18 July 2000	Information Amendment: 1 Pharm,/Tox report resubmitted (SN113)
28 July 2000	Information Amendment: 12 Pharm,/Tox reports (SN115)
02 October 2000	Information Amendment: Amendment to1 Pharm,/Tox report (SN118)
16 August 2001	Information Amendment: CMC manufacturing information (SN142)
04 October 2001	FDA information request (IND CMC)
01 November 2001	Information Amendment: 3 clinical study reports (SN155)
08 November 2001	Response to 04 October 2001 information request (IND CMC)
18 December 2001	End-of-Phase II Meeting
04 January 2002	Sponsors' minutes of 18 December 2001 End-of-Phase II Meeting (SN163)

IND 51,196 ACTIVITIES

Date	Activity
31 July 1996	Submitted original IND application with cross-reference to IND 51,126 for CMC, Pharm-Tox and Clinical information
14 August 1996	FDA acknowledged receipt of IND and assigned IND number: 51,196
10 October 1996	Information amendment: one pharm/tox report
18 November 1996	Information amendment: one pharm/tox report
16 June 1997	Sanofi provided Organon authorization to cross- reference IND 51,196 in its entirety
10 November 1997	Sanofi requested FDA guidance
20 November 1997	Sanofi provided clarification to the 10 November 1997 request for guidance
24 November 1997	FDA provided response to 10 November 1997 request for guidance
03 December 1997	Sanofi provided a response to FDA's 24 November 1997 guidance
05 December 1997	Telephone contact: FDA agreed with Sanofi's 03 December 1997 response
08 January 1998	FDA information request
27 January 1998	Response to 08 January 1998 information request
06 March 1998	Information Amendment: 1 Clinical report, 2 Pharm/Tox reports
04 August 1998	Information amendment: CMC
20 August 1998	Information amendment: 5 clinical study reports
14 September 1998	Telephone contact: FDA request for information
02 October 1998 (Exact date of faxed response not in database. Had to be prior to 2 October 1998 meeting)	Response to 14 September 1998 request for information
02 October 1998	Meeting between FDA and Sanofi/Organon to discuss pivotal nature of dose-ranging study
06 May 1999	FDA information request
08 June 1999	Response to 06 May 1999 FDA information request
10 June 1999	Telephone contact: FDA information request
10 June 1999	Partial response to 10 June 1999 FDA information request
11 June 1999	Completes response to 10 June 1999 FDA information request
24 June 1999	09 February 1999, End-of-Phase II meeting follow-up meeting. FDA request for information.
01 July 1999	FDA's minutes of the 24 June 1999 meeting
22 July 1999	Response to 24 June 1999 FDA request for information
08 September 1999	Request for FDA Guidance
20 September 1999	FDA response to 08 September 1999 request for guidance
21 September 1999	FDA comment on 24 June 1999 response to FDA request for information
26 October 1999	Response to 24 June 1999 FDA request for information and 21 September 1999 FDA comments. Request for FDA input.

Date	Activity
28 January 2000	Request for FDA input
14 February 2000	FDA response to 28 January 1999 request for input
27 July 2000	Telephone contact: request for FDA input
14 September 2001	FDA recommendations
01 November 2001	Response to FDA recommendations

PRE-NDA ACTIVITIES

Date	Activity
31 March 2000	CMC Pre-NDA Meeting
10 April 2000	FDA Meeting Minutes of 31 March 2000 CMC Pre-NDA Meeting
14 April 2000	Pre-NDA Technical Meeting
05 May 2000	FDA Meeting Minutes of 14 April 2000 Pre-NDA Technical Meeting
10 May 2000	Sponsor's Meeting Minutes of 14 April 2000 Pre-NDA Technical Meeting
26 May 2000	Sponsor's request for FDA review of discrepancies between FDA and sponsor's meeting minutes of the 14 April 2001 Pre-NDA Technical Meeting
28 August 2000	Proprietary name review request
21 November 2000	Request for early submission of NDA CMC and Non-Clinical sections
19 December 2000	Pre-submission of NDA Non-Clinical Pharm/Tox Section
27 December 2000	FDA Acknowledgement of 19 December 2000 submission
16 January 2001	Request for pediatric waiver for NDA
22 January 2001	Pre-submission of NDA CMC Section
02 February 2001	Pediatric waiver granted
15 February 2001	Alternate proprietary name review request

NDA 21-345 ACTIVITIES

Date	Activity
15 February 2001	NDA Submission
28 February 2001	Telephone contact: FDA Information Request
01 March 2001	Response to 28 February 2001 FDA Information Request
02 March 2001	FDA Acknowledgement of 15 February 2001 NDA submission
12 March 2001	Telephone contact: FDA Information Request;
19 March 2001	NDA given standard review designation
21 March 2001	Response to 12 March 2001 information request
30 March 2001	Telephone contact: FDA information request
04 April 2001	Telephone contact: FDA information request
09 April 2001	Response to 30 March 2001 and 04 April 2001 information requests
24 April 2001	NDA review designation changed to priority review
25 April 2001	Proprietary name "Arixtra" accepted
26 April 2001	Telephone contact: FDA information request
01 May 2001	Response to 26 April 2001 information request

31 May 2001	Telephone contact: FDA information request
05 June 2001	Telephone contact: FDA information request
05 June 2001	Response to 05 June 2001 information request
06 June 2001	Telephone contact: FDA information request
08 June 2001	Response to 31 May 2001 information request
11 June 2001	Telephone contact: FDA information request
15 June 2001	120-day Safety Update
18 June 2001	Telephone contact: FDA information request
18 June 2001	Response to 18 June 2001 information request
18 June 2001	Response to 06 June 2001 information request
20 June 2001	Response to 11 June 2001 information request
20 June 2001	Telephone contact: FDA information request
20 June 2001	Response to 20 June 2001 information request
26 June 2001	CMC discipline review letter: FDA information request
26 June 2001	Telephone Contact: FDA information request
02 July 2001	Telephone Contact: FDA information request
03 July 2001	Response to 02 July 2001 FDA information request
03 July 2001	Response to 26 June 2001 telephone contact information request
16 July 2001	Microbiology discipline review letter: FDA information request
20 July 2001	Response to 26 June 2001 CMC discipline review letter information request
25 July 2001	Partial response to 16 July 2001 Microbiology discipline review letter information request
31 July 2001	Completed response to 16 July 2001 Microbiology discipline review letter information request
01 August 2001	Telephone contact: FDA information request
01 August 2001	Response to 01 August 2001 information request
15 August 2001	Approvable letter
22 August 2001	Notice of intent to file an amendment to NDA in response to approvable letter
04 September 2001	Partial response to NDA approvable letter
07 September 2001	Telephone contact: FDA information request
07 September 2001	Response to 07 September 2001 information request
12 September 2001	Telephone contact: FDA information request
09 October 2001	Response to 12 September 2001 information request, completed response to 15 August 2001 approvable letter (resubmission)
19 November 2001	Telephone contact and facsimile: FDA information request
20 November 2001	Response to 19 November 2001 information request
05 December 2001	FDA meeting: FDA information request
06 December 2001	Response to 06 December 2001 information request
06 December 2001	Telephone contact: FDA information request
07 December 2001	Response to 06 December 2001 information request
07 December 2001	NDA approval

(12) In the opinion of the Applicant, United States Patent 4,818,816 is eligible for an extension of 1,116 days. The length of said extension was calculated as follows:

1.	The number of days for the testing phase as defined in 37 CFR 1.775 (c)(1)	1,642
2	The number of days for the approval phase as defined in 37 CFR 1.775(c)(2)	295
3	Total of line 1 and line 2	1,937
4.	The number of days of the period of line 2 which occurred prior to the issue date of the patent	0
5.	The number of days of the period of line 2 during which the Applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0
6.	Total of line 4 and line 5	0
7.	Total of line 3 less line 6	1,937
8.	The number of days of the period of line 1 which occurred prior to the issue date of the patent	0
9.	The number of days of the period of line 1 during which the Applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0
10.	The total of line 8 and line 9	0
11.	Total of line 7 less line 10	1,937
12.	The number of days from line 1	1,642
13.	The number of days from line 10	0
14.	The total of line 12 less line 13	1,642
15.	One half of line 14	821
16.	The total of line 11 less line 15	1,116
17.	The original expiration date of the patent	August 19, 2003

18.	The expiration date of the patent if extended by the number of days on line 16	September 8, 2006
19.	The date of the FDA final approval	December 7, 2001
20.	The limitation set forth in 37 CFR 1.775(d)(3)	14 years
21.	The number of years on line 20 added to the date on line 19	December 7, 2015
22.	The earlier of the dates on line 18 and line 21	September 8, 2006
23.	The original expiration date of patent	August 19, 2003
24.	The limitation set forth in 37 CFR 1.775(d)(5)	5 years
25.	The number of years on line 24 added to the date on line 23	August 19, 2008
26	The earlier of the dates on line 22 and line 25	September 8, 2006
27.	The original expiration date of the patent	August 19, 2003
28.	The number of days by which line 26 and line 27 differ	1,116

(13) Applicant acknowledges its duty to disclose to the Commissioner for Patents and the Secretary of Health and Human Services any information of which it is aware that is material to the determination of entitlement to the extension sought.

(14) The Commissioner is hereby authorized to charge to Deposit Account No. 19-0091 the prescribed fee of $1,120 under 37 CFR § 1.20(j), and to charge any additional fees which may be required, or credit any overpayment to said deposit account.

(15) Correspondence relating to this application should be directed to:

Paul E. Dupont
Sanofi–Synthelabo Inc.
9 Great Valley Parkway
Malvern, PA 19355

Telephone or facsimile communications relating to this application can be directed to the undersigned at the numbers listed below.

Respectfully submitted,

Sanofi-Synthelabo

Dated: January 29 2002

By
Paul E. Dupont
Agent for Applicant
Registration No. 27,438

Address:
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